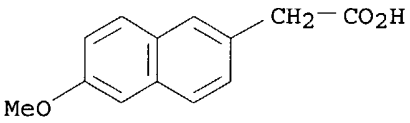
10/056,478

```
     (FILE 'HOME' ENTERED AT 14:11:22 ON 24 AUG 2004)

     FILE 'REGISTRY' ENTERED AT 14:12:06 ON 24 AUG 2004
                E 6-MNA/CN
                E ?MNA/CN
                E MNA/CN
L1            3 S E3

     FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:14:06 ON 24
     AUG 2004
L2          128 S 6-MNA

     FILE 'REGISTRY' ENTERED AT 14:15:09 ON 24 AUG 2004
                E 6-METHOXY-2-NAPHTHYLACETIC ACID/CN
L3            3 S E3-E5
                E OXYCODONE/CN
L4            2 S E2-E3

     FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS, CAOLD, USPAT2, USPATFULL,
     BIOTECHNO, BIOBUSINESS' ENTERED AT 14:17:56 ON 24 AUG 2004
L5            9 S L3 AND L4
L6           34 S 6-MNA AND L4
L7           26 S L6 NOT L5

     FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS, CAOLD' ENTERED AT 14:20:50
     ON 24 AUG 2004
L8          333 S L3 OR 6-MNA
L9           64 S L8 AND IBUPROFEN?
L10          31 S L9 AND (CYCLOXYGEN? OR COX?)
L11          22 DUP REM L10 (9 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 14:24:13 ON 24 AUG 2004

     FILE 'CAPLUS, EMBASE, BIOSIS, MEDLINE, WPIDS' ENTERED AT 14:25:38 ON 24
     AUG 2004
L12         332 S L3 OR 6-MNA
L13         129 S L12 AND (ASPIRIN? OR IBUPROFEN? OR NSAID?)
L14          44 S L13 AND (GASTROINTEST? OR GI)
L15          28 DUP REM L14 (16 DUPLICATES REMOVED)
L16        1169 S (BURCH, R? OR BURCH R?)/AU,IN
L17         226 S (GOLDENHEIM, P? OR GOLDENHEIM P?)/AU,IN
L18         107 S (SACKLER, R? OR SACKLER R?)/AU,IN
L19        1449 S L16 OR L17 OR L18
L20           2 S L19 AND (L2 OR 6-MNA)

=>
```

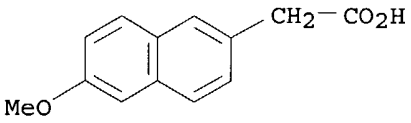
L3 ANSWER 1 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 141969-30-4 REGISTRY
CN 2-Naphthaleneacetic acid, 6-methoxy-, potassium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **6-Methoxy-2-naphthylacetic acid potassium salt**
MF C13 H12 O3 . K
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)
CRN (23981-47-7)



● K

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 141969-29-1 REGISTRY
CN 2-Naphthaleneacetic acid, 6-methoxy-, sodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **6-Methoxy-2-naphthylacetic acid sodium salt**
MF C13 H12 O3 . Na
SR CA
LC STN Files: CA, CAPLUS
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study)
CRN (23981-47-7)

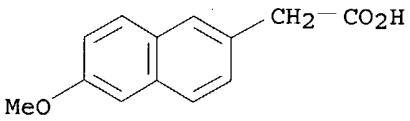


● Na

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2004 ACS on STN
RN 23981-47-7 REGISTRY
CN 2-Naphthaleneacetic acid, 6-methoxy- (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2-(6-Methoxy-2-naphthyl)acetic acid
CN 6-Methoxy-2-naphthaleneacetic acid
CN **6-Methoxy-2-naphthylacetic acid**
CN BRL 10720

FS 3D CONCORD
MF C13 H12 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PS, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PRP (Properties); USES (Uses)



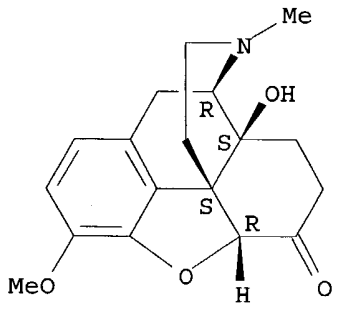
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

130 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
130 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L4 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 124-90-3 REGISTRY
CN Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride, (5α)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Codeinone, 7,8-dihydro-14-hydroxy-, hydrochloride (6CI, 7CI)
CN Morphinan-6-one, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl-, hydrochloride (8CI)
OTHER NAMES:
CN 14-Hydroxydihydrocodeinone hydrochloride
CN 4,5α-Epoxy-14-hydroxy-3-methoxy-N-methyl-6-oxomorphinan hydrochloride
CN Dihydro-14-hydroxycodeinone hydrochloride
CN Dihydrone hydrochloride
CN Dihydrooxycodeinone hydrochloride
CN Dinarkon
CN Endone
CN Eubine
CN Eucodal
CN Eukodal
CN Eutagen
CN Oxikon
CN Oxycod
CN **Oxycodon hydrochloride**
CN Oxycodone hydrochloride
CN Oxycon
CN OxyContin
CN Oxygesic
CN Oxykodal
CN Oxykon
CN Pancodine
CN Roxicodone
CN Stupenone
CN Supeudol
CN Tecodin
CN Tecodine
CN Tekodin
CN Thecodin
CN Thecodine
CN Thekodin
FS STEREOSEARCH
DR 13699-57-5, 30777-15-2
MF C18 H21 N O4 . Cl H
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, HSDB*, IPA, MRCK*, MSDS-OHS, PIRA, PROMT, PROUSDDR, PS, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
CRN (76-42-6)

Absolute stereochemistry.



● HCl

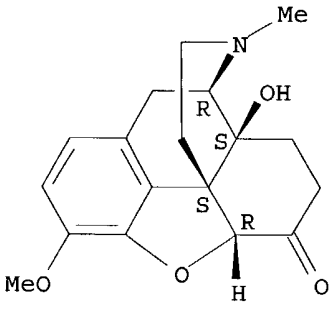
314 REFERENCES IN FILE CA (1907 TO DATE)
315 REFERENCES IN FILE CAPLUS (1907 TO DATE)
18 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L4 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
RN 76-42-6 REGISTRY
CN Morphinan-6-one, 4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-, (5α)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Codeinone, 7,8-dihydro-14-hydroxy- (6CI, 7CI)
CN Morphinan-6-one, 4,5α-epoxy-14-hydroxy-3-methoxy-17-methyl- (8CI)
OTHER NAMES:
CN (-)-Oxycodone
CN 14-Hydroxydihydrocodeinone
CN 3-O-(Methyl)oxymorphone
CN 6-Oxo-14-hydroxy-7,8-dihydrocodeine
CN 7,8-Dihydro-14-hydroxycodeinone
CN Dihydro-14-hydroxycodeinone
CN Dihydrohydroxycodeinone
CN Dihydrone
CN NSC 19043
CN Oxanest
CN Oxicon
CN Oxycodeinone
CN **Oxycodone**
CN Oxymorphone 3-methyl ether
FS STEREOSEARCH
MF C18 H21 N O4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological

study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

747 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
752 REFERENCES IN FILE CAPLUS (1907 TO DATE)
32 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

=>

L11 ~~ANSWER 17 OF 22~~ CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
AN 1997:32962 CAPLUS
DN 126:99032
TI Nonsteroidal antiinflammatory drugs and uncoupling of mitochondrial oxidative phosphorylation
AU Mahmud, Taher; Rafi, Sue S.; Scott, David L.; Wrigglesworth, John M.; Bjarnason, Ingvar
CS Academic and Clinical Rheumatology, King's College Hospital, London, SE22 8PT, UK
SO Arthritis & Rheumatism (1996), 39(12), 1998-2003
CODEN: ARHEAW; ISSN: 0004-3591
PB Lippincott-Raven
DT Journal
LA English
AB There is a lack of correlation between cyclooxygenase (**COX**) inhibition and nonsteroidal antiinflammatory drug (NSAID)-induced gastrointestinal (GI) damage; it has been suggested that mucosal damage may be initiated by a "topical" action of NSAIDs involving mitochondrial injury. We evaluated the effect of a range of NSAIDs and related compds. on mitochondrial function and assessed the differences between them in relation to their physicochem. properties. Stimulation of respiration, as an indicator of mitochondrial uncoupling, was measured in isolated coupled rat liver mitochondrial prepns., using an oxygen electrode. Conventional NSAIDs and acidic prodrugs all had stimulatory effects on mitochondrial respiration at micromolar concns. (0.02-2.7 μM); higher concns. were inhibitory. The uncoupling potency was inversely correlated with drug pKa ($r = -0.87$). Drugs known to have good GI tolerability, including modified flurbiprofen (dimeroflurbiprofen and nitrobutylflurbiprofen), nabumetone (a non-acidic prodrug), and non-acidic highly selective **COX**-2 inhibitors, did not cause uncoupling. The ability to uncouple mitochondrial oxidative phosphorylation is a common characteristic of antiinflammatory agents with an ionizable group. Modification or absence of an ionizable moiety reduces the effect on mitochondria and could lead to improved NSAID GI safety.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 18 OF 22 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 96327479 EMBASE
DN 1996327479
TI The clinical implications of inhibition of the inducible form of cyclo-oxygenase.
AU Richardson C.; Emery P.
CS Dept. of Rheumatology Rehabilitation, University of Leeds, 36 Clarendon Road,Leeds LS2 9NZ, United Kingdom
SO Drug Safety, (1996) 15/4 (249-260).
ISSN: 0114-5916 CODEN: DRSAEA
CY New Zealand
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
048 Gastroenterology
LA English
SL English
AB There are 2 isoenzymes of cyclo-oxygenase (**COX**). There is a constitutive enzyme **COX**-1 which has a wide tissue distribution. In addition there is an inducible enzyme **COX**-2 which has a restricted tissue distribution. The inducible enzyme **COX**-2 is responsible for the generation of prostaglandins at sites of tissue inflammation and its inhibition is associated with an anti-inflammatory

action. The constitutive enzyme, **COX**-1 is responsible for the production of prostaglandins with multiple functions. One well known and clinically important function is the gastroprotective effect of the prostaglandins produced in the gastric mucosa. While selective **COX** -2 inhibition may be associated with a reduced incidence of gastric adverse effects, a concern remains that its inhibition at other locations may be associated with other adverse effects.

L11 ANSWER 19 OF 22 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
AN 1996:333511 CAPLUS
DN 125:25851
TI Selective inhibition of human cyclooxygenase-2 by meloxicam
AU Churchill, L.; Graham, A.G.; Shih, C.-K.; Pauletti, D.; Farina, P.R.; Grob, P.M.
CS Department of Inflammatory Diseases, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
SO Inflammopharmacology (1996), 4(2), 125-135
CODEN: IAOAES; ISSN: 0925-4692
PB Kluwer
DT Journal
LA English
AB Human cyclooxygenase-1 (hCOX-1) and -2 were expressed in stable transfected COS A.2 cells and in insect cells using a Sf9 baculovirus expression system. Inhibition of **COX** activity was examined using both whole cell and microsomal assays. **Ibuprofen**, naproxen, **6-MNA**, diclofenac and indomethacin were selective for hCOX-1 or were equipotent inhibitors for **COX**-1 and **COX** -2. Piroxicam was equally inhibitory for both enzymes in the whole cell assay while it preferentially inhibited hCOX-2 in the microsomal assay. However, maximal inhibition of hCOX-2 by piroxicam plateaued at 60%. Nimesulide was equipotent in the whole-cell assay but was five-fold selective for hCOX-2 in the microsomal assay. Meloxicam preferentially inhibited hCOX-2 in the whole cell assay at concns. of 0.01 to 1 μmol/L but was an equipotent inhibitor of both enzymes at higher concns. In the microsomal assay, meloxicam exhibited high selectivity for hCOX-2 (75-fold). The preferential inhibition of hCOX-2 by meloxicam may explain the favorable gastrointestinal profile observed for meloxicam compared with other nonsteroidal antiinflammatory agents.

L11 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AN 1995:489958 BIOSIS
DN PREV199598504258
TI Selective inhibition of cyclooxygenase-2: Diaryl heterocycles vs classical NSAIDS.
AU Pinto, Donald J. [Reprint author]; Pitts, William J.; Copeland, Robert A.; Covington, Maryanne B.; Trzaskos, James; Magolda, Ronald
CS The Du Pont Merck Pharmaceutical Company, Inflammatory Disease Res., PO Box 80353, Wilmington, DE 19880-0353, USA
SO Medicinal Chemistry Research, (1995) Vol. 5, No. 5, pp. 394-398.
ISSN: 1054-2523.
DT Article
General Review; (Literature Review)
LA English
ED Entered STN: 9 Nov 1995
Last Updated on STN: 14 Dec 1995
AB This review discusses the in vitro and in vivo activities of selected anti-inflammatory diaryl heterocycles, as compared with selected classical NSAIDS. The diaryl heterocycle tiflamizole is a selective inhibitor of **COX1** and shares the liabilities of classical NSAIDS while DuP697 is a selective inhibitor of **COX2** and exhibits a unique biological profile.

=>

L15 ANSWER 22 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
AN 1996:333511 CAPLUS
DN 125:25851
TI Selective inhibition of human cyclooxygenase-2 by meloxicam
AU Churchill, L.; Graham, A.G.; Shih, C.-K.; Pauletti, D.; Farina, P.R.; Grob, P.M.
CS Department of Inflammatory Diseases, Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA
SO Inflammopharmacology (1996), 4(2), 125-135
CODEN: IAOAES; ISSN: 0925-4692
PB Kluwer
DT Journal
LA English
AB Human cyclooxygenase-1 (hCOX-1) and -2 were expressed in stable transfected COS A.2 cells and in insect cells using a Sf9 baculovirus expression system. Inhibition of COX activity was examined using both whole cell and microsomal assays. **Ibuprofen**, naproxen, **6-MNA**, diclofenac and indomethacin were selective for hCOX-1 or were equipotent inhibitors for COX-1 and COX-2. Piroxicam was equally inhibitory for both enzymes in the whole cell assay while it preferentially inhibited hCOX-2 in the microsomal assay. However, maximal inhibition of hCOX-2 by piroxicam plateaued at 60%. Nimesulide was equipotent in the whole-cell assay but was five-fold selective for hCOX-2 in the microsomal assay. Meloxicam preferentially inhibited hCOX-2 in the whole cell assay at concns. of 0.01 to 1 μmol/L but was an equipotent inhibitor of both enzymes at higher concns. In the microsomal assay, meloxicam exhibited high selectivity for hCOX-2 (75-fold). The preferential inhibition of hCOX-2 by meloxicam may explain the favorable **gastrointestinal** profile observed for meloxicam compared with other nonsteroidal antiinflammatory agents.

L15 ANSWER 23 OF 28 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
AN 1996:177634 CAPLUS
DN 124:277519
TI New insight into **NSAID**-induced gastropathy
AU Spangler, R. S.
CS Worldwide Strategic Produce Development, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, USA
SO Inflammopharmacology (1995), 3(4), 347-50
CODEN: IAOAES; ISSN: 0925-4692
PB Kluwer
DT Journal; General Review
LA English
AB A review with 11 refs. The objective was to assess the impact of nabumetone's pharmacol. profile on gastric safety. Direct topical uptake of nabumetone by the gastric mucosa was assessed via autoradiog. The opportunity for nabumetone to cause indirect topical damage to the **gastrointestinal** tract was determined by examining the ability of 6-methoxy-2-naphthylacetic acid (**6-MNA**) to be secreted in the bile. The ability for **6-MNA** to cause damage to the gastric mucosa via the systemic circulation was assessed via the preferential activity of **6-MNA** on cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Nabumetone was shown not to exhibit direct uptake by the gastric mucosa when administered orally. **6-MNA**, the active metabolite of nabumetone, was not found to undergo enterohepatic circulation. **6-MNA** was found to act preferentially on COX-2. Nabumetone does not cause direct topical damage to the gastric mucosa because it is a nonacidic prodrug that will not concentrate in the gastric mucosa via "ion trapping". **6-MNA**, the active metabolite of nabumetone, does not recirculate in the bile, and therefore will not cause damage to the gastric mucosa via secretion into the bile and reflux back into the stomach. Finally, **6-MNA** has a low propensity to cause damage to the

gastric mucosa via the systemic circulation due to its preferential inhibition of COX-2.

L15 ANSWER 24 OF 28 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95153563 EMBASE
DN 1995153563
TI Actions and toxicity of nonsteroidal anti-inflammatory drugs.
AU Simon L.S.
CS Department of Medicine, New England Deaconess Hospital, 110 Francis Street,Boston, MA 02215, United States
SO Current Opinion in Rheumatology, (1995) 7/3 (159-166).
ISSN: 1040-8711 CODEN: CORHES
CY United States
DT Journal; General Review
FS 030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The use of nonsteroidal anti-inflammatory drugs (**NSAIDs**) continues to grow, despite the known potential toxic risks associated with it, probably because these drugs palliate pain and inflammation and are relatively well tolerated. Unfortunately, **NSAID** use has not been shown to have long-term beneficial effects on the natural history of inflammatory diseases. Regardless, the **NSAID** market has reached the 2.2 billion dollar mark, with 73,000,000 prescriptions written yearly throughout the world. Although individual toxic events are relatively rare, the large number of **NSAID** prescriptions ensures that all the possible potential adverse events will likely be encountered by some patients. Over the past year, interesting additions to the literature have been made regarding the mechanisms of action as well as adverse reactions associated with **NSAIDs**.

L15 ANSWER 25 OF 28 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 94122329 EMBASE
DN 1994122329
TI Nabumetone: A clinical appraisal.
AU Helfgott S.M.
CS Brigham and Women's Hospital, 45 Francis St.,Boston, MA 02115, United States
SO Seminars in Arthritis and Rheumatism, (1994) 23/5 (341-346).
ISSN: 0049-0172 CODEN: SAHRBF
CY United States
DT Journal; General Review
FS 006 Internal Medicine
030 Pharmacology
031 Arthritis and Rheumatism
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Nonsteroidal antiinflammatory drugs (**NSAIDs**) have long been used as therapy for arthritis patients. However, in some patients these drugs can cause **gastrointestinal** hemorrhage, perforation, or ulcer through direct topical effects, enterohepatic recirculation, and systemic effects. In an effort to address this problem, new **NSAIDs** have been developed. Nabumetone, which belongs to a new class of **NSAID**, is a nonacidic agent that has been associated with a low incidence of peptic ulcer. This article examines available clinical data on nabumetone, including studies on **gastrointestinal** safety and effectiveness in osteoarthritis and rheumatoid arthritis patients, and data that may

provide an explanation for nabumetone's low incidence of ulceration.

L15 ANSWER 26 OF 28 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 10
AN 93123898 EMBASE
DN 1993123898
TI Nabumetone: A 'nonacidic' nonsteroidal antiinflammatory drug.
AU Dahl S.L.
CS Gold IV Unit M4213, School of Medicine, University of Missouri, 2411 Holmes,Kansas City, MO 64108, United States
SO Annals of Pharmacotherapy, (1993) 27/4 (456-463).
ISSN: 1060-0280 CODEN: APHRER
CY United States
DT Journal; General Review
FS 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English; Spanish; French
AB OBJECTIVE: To review the pharmacology, pharmacokinetic disposition, dosage recommendations, adverse effects, drug interactions, and efficacy of nabumetone in patients with selected rheumatic disorders and soft-tissue injuries. DATA SOURCES: Data from scientific literature were extracted, evaluated, and summarized for presentation. A MEDLINE search was conducted using the following indexing terms: antiinflammatory agents, nonsteroidal, nabumetone, rheumatoid arthritis (RA), and osteoarthritis (OA). Studies evaluating nabumetone reported in articles, abstracts, or proceedings involving human subjects were considered for inclusion. STUDY SELECTION: Special consideration was given to clinical studies using double-blind, randomized, parallel, controlled designs. Studies comparing the effectiveness and safety of nabumetone with placebo and other nonsteroidal antiinflammatory drugs (**NSAIDs**) were included. DATA EXTRACTION: Data from human studies published in the English language were evaluated. Trials were assessed according to study design, sample size, and description of outcomes. DATA SYNTHESIS: Nabumetone is a nonacidic prodrug that is metabolized to an active nonsteroidal antiinflammatory moiety, 6-methoxy-2-naphthylacetic acid (**6- MNA**). **6-MNA** is a structural analog of naproxen. Like naproxen and other **NSAIDs**, **6-MNA** possesses analgesic, antipyretic, and antiinflammatory activity. **6-MNA** has a prolonged elimination half-life, ranging from 17 to 74 hours, which allows for once-daily dosing. The efficacy of nabumetone for treating symptoms of RA and OA has been established in controlled clinical trials. Nabumetone also has been studied in ankylosing spondylitis and soft-tissue injuries. Adverse effects associated with nabumetone are similar to those associated with other **NSAIDs**. **Gastrointestinal** reactions occur most frequently in the form of abdominal pain or indigestion, nausea, or vomiting. Central nervous system adverse effects occur less frequently, and are followed in order of occurrence by rashes. CONCLUSIONS: Nabumetone is a prodrug metabolized to an active metabolite structurally related to naproxen. Studies have demonstrated the efficacy of nabumetone, but no advantages over the many other **NSAIDs** now available.

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AN 92360325 EMBASE
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TI The unique pharmacologic profile of nabumetone.
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CS SmithKline Beecham Pharmaceuticals, Coldharbour Road,Harlow, Essex CM19 5AD, United Kingdom
SO Journal of Rheumatology, (1992) 19/SUPPL. 36 (13-19).
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CY Canada
DT Journal; Conference Article
FS 031 Arthritis and Rheumatism
030 Pharmacology
037 Drug Literature Index
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LA English
SL English
AB Nabumetone is a novel nonsteroidal antiinflammatory drug (**NSAID**) with a unique pharmacologic profile. It is nonacidic and demonstrates minimal prostaglandin synthesis inhibition. Because it is nonacidic, nabumetone cannot dissociate in the stomach after oral administration. In contrast, acidic **NSAID** (active cyclooxygenase inhibitors) can dissociate and concentrate by 'ion trapping' in the gastric mucosa, inhibit prostaglandin synthesis and, therefore, cause topically induced erosive mucosal damage. After absorption, nabumetone is converted by first pass metabolism to the active metabolite, 6-methoxy-2-naphthylacetic acid (6MNA), an effective inhibitor of prostaglandin synthesis. 6MNA is hepatically, not renally, cleared and differs from other **NSAID** because it does not undergo enterohepatic circulation in animals or man. This is thought to contribute to its apparent lack of severe **gastrointestinal** irritancy. The pharmacologic profile of nabumetone can be summarized in terms of the very large 'therapeutic ratio'in comparison with other **NSAID**.

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